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The attached documents are exact copies of the European patent application described on the following page, as originally filed.

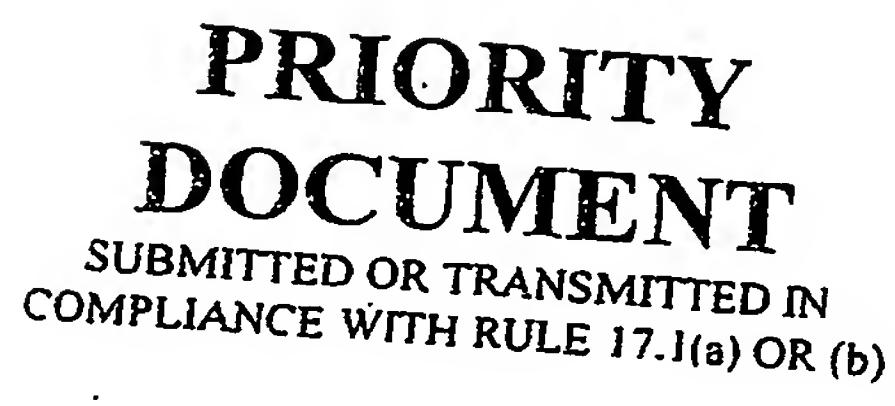
Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

03013899.4

REC'D 29 JUL 2004

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Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk



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(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

omega-substituted acid flavonoidester

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Esters of flavonoids with ω -substituted C6 to C22 fatty acids

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The invention refers to esters of flavonoids, such as flavones, flavonols, flavanones, flavanols, flavanolols, isoflavones, anthocyanins, proanthocyanidins, chalcones, aurones, and hydroxycoumarins conjugated by an ester bond to a ω -substituted C6 to C22 fatty acid.

15 In addition it refers to cosmetic and pharmaceutical formulations and nutritional products comprising these flavonoid derivatives and the use of the flavonoid esters.

20

State of the art

Flavonoids are a class of naturally occurring polyphenols in plants. They are benzo- γ -pyron derivatives and can be classified into several groups (flavones, flavonols, flavanones, flavanols, flavanolols, isoflavones, anthocyanins, proanthocyanidins, chalcones, aurones, hydroxycoumarins) according to the presence of different substituents on the rings and the oxidative degree of ring C (figure 1). These flavonoids may also exist in glycoside or aglycon form and other modifications such as methylation or acylation of hydroxyl groups increase the diversity of these molecules and their properties.

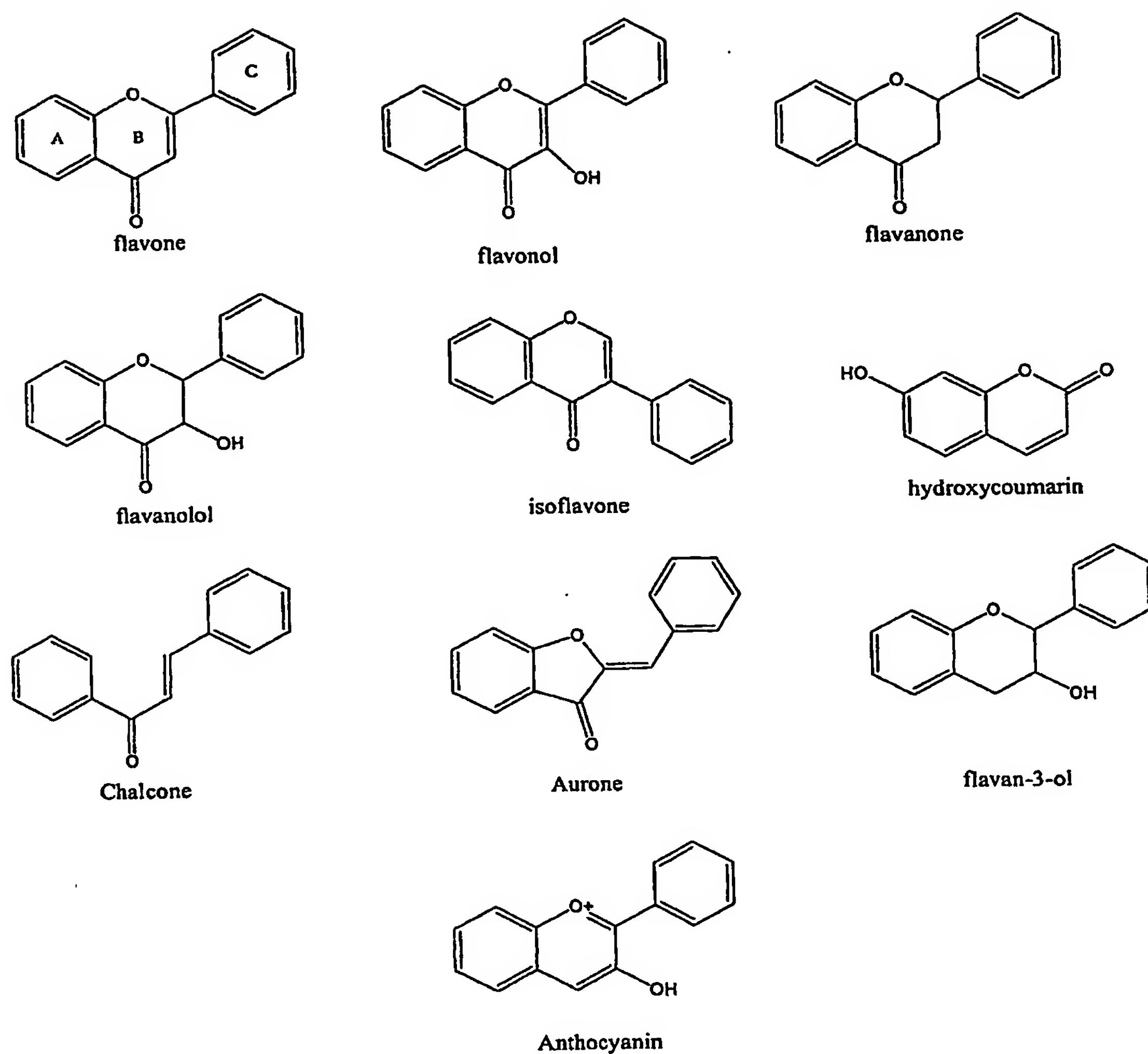


Figure 1: Different groups of flavonoid derivatives

For many years flavonoids have been known for their biological activities. Their main properties are antioxidant activities and enzyme inhibiting activities. They are already used in cosmetic and pharmaceutical formulations for applications in the following fields: anti-erythema, anti-blotchiness, sensitive skin, draining, slimming, anti-wrinkles, stimulation of the extracellular matrix, toning up, skin elasticity, anti-ageing, cardiovascular diseases, veinotonic, inflammation, allergy, antiviral, antibacterial properties or in general as stabilizing or protecting therapeutic agents.

For reasons of their anti-radical activity combined with their absorption spectrum in the UV range, flavonoids may be of interest in the prevention of photo-oxidative skin damage. UV radiation is one aspect of environmental stress on the skin. The main UV radiation attacking the skin is in the range of 290 – 320 nm (UVB) reaching the dermis and upper dermis and

320-400 nm (UVA), the most penetrating radiation that affects the dermis. Nuclear or mitochondrial DNA damages, generation of reactive oxygen species which are responsible for lipid and protein damage, are induced by UVA and/or UVB radiation and involve immediate and transient biological responses, for example, inflammation, sunburn, loss of skin elasticity,
5 and delayed and chronic biological responses such as photoaging, or photocarcinogenesis. However Saija et al. (1998, International Journal of Pharmaceutics, 175, 85) have demonstrated that flavonoids were ineffective in formulations.

Moreover, the application of flavonoids in cosmetic, pharmaceutical preparations and nutrition
10 is limited by their low solubility and stability.

The solubility of flavonoids (glycosylated and aglycon) in both aqueous and lipophilic phases is low. Thus it is very difficult to incorporate flavonoids in cosmetic, pharmaceutical or nutraceutical formulations. A second drawback is a poor bioavailability of flavonoids.
15 Flavonoids are unstable due to the presence of many hydroxyl groups in their structure. They are degraded by light, oxygen or oxidizing agents and high temperature.

To improve the UV-protection properties of flavonoids, a combination by acylation or alkylation of flavonoids, particularly tiliroside, with aromatic compounds known for their UV-filter properties – for example dibenzoylmethane derivatives or benzoyl derivatives - has been described in the International application WO 02069926. The linking of flavonoids to UV-filter molecules increases the stability of UV-filters. In the European application EP 1205475 aglycon flavonoids were also modified with the same UV-filter. These compounds possess the properties of both molecules: the antioxidant and enzyme inhibitor activities of flavonoids and the UV absorption properties of a filter.
25

In the US-patent US 4255336 derivatives of cyanidan-3-ol with organic carboxylic acid , carbonic acid, sulphonic acid were described in respect of their activity regarding the prevention of hepatic necrosis and lipoperoxydation. These compounds could protect the tissue by the inhibition of the degradation of collagen by collagenase.
30

Different solutions have been proposed to solve the problem of instability of flavonoids such as encapsulation or addition of antioxidants. Another described way to increase the stability and the lipophilicity of flavonoids is their acylation with fatty acids by chemical or enzymatic means. In the French patent FR 2706478 therapeutical and cosmetic formulations containing esters of flavanol and procyanolidic oligomers and fatty acid were described. The acylation of phenolic groups has increased the stability of the formulation in respect of color without decreasing the antioxydant activity. In FR 2778663 fatty esters of flavonoids were synthesized
35

by chemical means. The resulting flavonoid esters were stabilized in preparations and emulsions and their anti-radical activities were preserved.

The activity of enzyme inhibition was also increased by the acylation of flavonoids with fatty acids. This is a result of a higher degree of penetration through the cell membrane.

5

In the US-patent US 5844061 flavonol and procyanolide oligomers were rendered liposoluble and stable by protecting the hydroxyl groups by esterification with fatty acid or aryl acid. The antiradical and antioxidant properties of these esters can be exploited in therapeutic, cosmetic and dietetic fields.

10

The International patent application WO 00/44757 discloses hydrophilic and lipophilic hesperetin acylated with an organic or inorganic salt of acid or with fatty acid or substituted fatty acid or aromatic acid in order to increase the bioavailability of hesperetin for pharmaceutical application.

15

The bioavailability of flavonoids may also be improved by increasing their aqueous solubility. Hydrophilic quercetin, apigenin, genistein were obtained by linking a phosphorylated sugar (inositol phosphate) directly or by a short carbon chain (succinate ester). This method increases the aqueous solubility of quercetin due to a linkage with a polar group without diminishing its cytotoxic and antiproliferative activity (WO 96/21440).

In WO 99/63995 the bioavailability of isoflavones was increased by improving their aqueous solubility. This was accomplished by attaching a polar group. Isoflavones were esterified on an alcohol functionality of aglycon part using a carboxylic acid group or a phosphoric acid group possessing a polar group directly attached to acid or indirectly linked to a short carbon chain. Succinate, glutarate, adipate and phosphate ester were described as good solubilizer with biological compatibility. Esterified isoflavones can be converted into free isoflavone in biological media by hydrolyzing the ester bond by various enzymes. The esterified isoflavones can be used in nutritional supplements and pharmaceutical preparations as phytoestrogen, antiangiogenic, antioxidant, anticancer and against ultraviolet skin damage.

Microcapsules of flavonoids have also been obtained by interfacial cross-linking of flavonoids with diacide (FR 2715582). Microcapsules were prepared by mixing an aqueous solution of flavonoid with an organic solution of diacide under vigorous stirring and at elevated pH. The stabilized polyphenol retains its activities.

In the German patent application DE 10019235 glycosylated flavonoids and isoflavones acylated with fatty acid or arylaliphatic acid are claimed for cosmetic and pharmaceutical application.

- 5 Dicarboxylic acids, having carboxylic groups at the opposite ends of the hydrocarbon chain represent an interesting class of fatty acid derivatives with bactericidal properties and enzyme inhibition activity. Moreover, the majority of these acids are unable to rapidly cross liposome membranes. Azelaic acid is already used as a cosmetic and therapeutic agent for bleaching of hair, for inhibiting the activity of protease inducing scales and tyrosinase, as anti-acne, antiaging, and as skin lightening agents, and has some effects in certain skin disorders.
- 10

Accordingly it is an object of the present invention to provide new molecules that combine the properties of flavonoids and ω -substituted C6 to C22 fatty acids with improved biological properties, chemical and physico-chemical stability. These molecules should protect skin, mucous membranes and scalp from damages by UV-radiation and thereby prevent ageing of the skin.

15 It is another object of the invention to provide formulations comprising these flavonoid derivatives with improved physico-chemical properties and high bioavailability.

20

Detailed description of the invention

- 25
- The present invention relates to flavonoid esters with ω -substituted C6 to C22 fatty acids.
 - In addition it relates to nutritional, cosmetic or pharmaceutical compositions containing these flavonoid esters and compositions wherein these flavonoid esters are incorporated in liposomes or microcapsules.
 - Further on, the invention concerns the use of flavonoid esters with ω -substituted C6 to C22 fatty acids to protect skin and scalp against damages caused by UV-radiation, such as mitochondrial or nuclear DNA damage which is resulting in accelerated skin aging, it concerns the protection against oxidative stress, environmental stress or pollutants, and the use as anti-inflammatory agent.
- 30
- Surprisingly it has been found that the esters of flavonoids with ω -substituted C6 to C22 fatty acids have the property to protect the skin cells against damages caused by UV radiation. As shown in the examples, we have found that the esters of flavonoids according to the invention protect skin cells against UVA and UVB radiation in a more effective manner than the flavonoids alone. Moreover, these esters demonstrated their property to stimu-
- 35

late the GSH metabolism of human skin cells after UVA irradiation, i.e., to stimulate their cellular defenses. They have also anti-inflammatory and soothing properties as demonstrated by the inhibition of released PGE2 after UVB irradiation.

- 5 ➤ Thereby these flavonoid esters may be used to protect the skin and scalp and/or to fight UV and sun damages, erythema, sunburn, mitochondrial or nuclear DNA damages, to prevent or fight photo-ageing, providing improvement for signs of ageing as skin wrinkles, elasticity loss and a decrease in skin thickness.
- 10 ➤ They may also be used to protect skin, scalp and/or hair shafts and fight oxidative or stress damages, to protect skin, scalp and/or hair shafts from environmental stress such as pollutants, chemicals.

15 They may be used to improve the appearance of the skin with local inflammations or microinflammations. Moreover, they may be used to treat sensitive or irritated skin or scalp, as appeasing and anti-itching agent as cosmetic agents to improve sensitive skin, reduce particularly scalp itching, or modify the melanin synthesis in human skin.

20 Since the flavonoid esters still exhibit the activities of the pure flavonoids, the invention also allows their use as anti-free radicals, anti-oxidant and anti-blotchiness agents, for draining treatment, for slimming treatment, for anti-wrinkle treatment, as stimulator of the synthesis of elastin and other extracellular matrix elements and in toning up compositions. They may also be used in compositions for applications related to cardiovascular diseases, veinotonic effects, inflammation disorders, allergies, as antiviral and antibacterial agents 25 or as stabilizing or protecting therapeutical agents.

- The disclosed flavonoid esters show a very good chemical stability.
- 30 ➤ Flavonoid esters with ω -substituted C6 to C22 fatty acids have a better solubility in lipophilic vehicles, and so they can be easily incorporated in cosmetic, dermatological, pharmaceutical formulations and as nutritional supplements.
- 35 ➤ Compared to compositions disclosed in the International patent application WO 99/63995 the bioavailability of isoflavones was further increased by improving their lipophilic solubility. This was accomplished by attaching not only a polar group, but by inserting a C6 to C 22 chain of the fatty acid. Flavonoid esters with ω -substituted C6 to C22 fatty acids can directly be dissolved in the oil phase of the formulations, or be totally or partially incorporated in liposomes or microcapsules.

- The incorporation in liposomes or microcapsules has the advantage that the release of the active flavonoid esters can be controlled. Especially the disclosed lipophilic flavonoid derivatives are easily incorporated in delivery systems for controlled release.
- 5 These delivery systems have a very good physico-chemical stability due to the solubility profile of the special flavonoid esters which also results in an improved bioavailability.
- The effective quantity of the disclosed flavonoid esters in formulations is 0.0001 to 10 wt %, preferably 0.001 to 5 wt %, most preferably 0.01 to 2 wt % based on the final composition.

10

Flavonoids

- The term flavonoid represents an aglycone or glycosylated form of the following class of polyphenols chosen from the group consisting of flavones, flavonols, flavanones, flavanols, flavanolols, isoflavones, anthocyanins, proanthocyanidins, chalcones, aurones, hydroxycoumarins. Preferably the glycosylated form is chosen.
- 15 ➤ Preferably the flavonoids are selected from the group consisting of aglycones or the glycosylated form of kampferol, phloretin, apigenin, luteolin, apigenin, quercetin, hesperetin, naringenin, cyanidin, gossypetin, genistein, daidzein, catechin, epicatechin, fisetin, liquiritigenin and esculetin. More preferably, the flavonoids are selected from the group consisting of the glycosylated forms of quercetin as rutin, glycosylated form of hesperetin as hesperidin, glycosylated form of naringenin as naringin, and glycosylated form of esculetin as esculin.
- 20
- 25

ω-substituted C6 to C22 fatty acids

- The term ω-substituted C6 to C22 fatty acid represents a saturated or unsaturated, linear or branched aliphatic carboxylic acid with 6 to 22 carbon atoms having one or more polar groups – besides the carboxylic acid group – on carbon atoms anywhere in the chain, preferably at the terminal carbon atom. Preferably these fatty acids have 8 to 18 carbon atoms.
- 30 ➤ This polar group may be :
 - (a) a derivative of carboxylic acid chosen from the group consisting of a carboxylic acid COOH; an amide CONR'₂ or CONR'₃S⁻ wherein R' is a hydrogen atom, a saturated or unsaturated, linear or branched alkyl C1-C6 radical, or an aryl, aralkyl or aralkylene radical and S⁻ a counterion; a COHal wherein Hal is a halogen atom and a COSH. Examples of this ω-substituted C6 to C22 fatty acid group are octanedioic acid, azelaic acid, decandioic acid, dodecandioic acid, hexadecandioic acid and octadecandioic acid.

- (b) a thiol or an alkylthioalkyl group such as 11-mercaptoundecanoic acid,
 (c) a primary, secondary, tertiary amine or a quaternium salt of hydrogen atom, a saturated or unsaturated, linear or branched alkyl C1-C6 radical, or an aryl, aralkyl or aralkylene radical such as 11-aminoundecanoic acid,
 5 (d) an halogen atom,
 (e) a nitro NO₂ group,
 (f) an organic or inorganic phosphoric or sulphuric acid,
 a hydroxyl group or an alkoxyalkyl group, the hydroxyl group being only on the terminal carbon atom, such as 16-hydroxyhexadecanoic acid.
 10 The most preferred derivatives are the derivatives of carboxylic acids (group (a)), especially dicarboxylic acids.

The ω -substituted C6 to C22 fatty acid is also represented by a di-carboxylic acids linked to a flavonoid by an ester bond on one of its carboxylic group, i.e. HOOC-X-C(=O)-O-Flavonoid,
 15 wherein X is a saturated or unsaturated, linear or branched alkyl radical (C₄ – C₂₀).

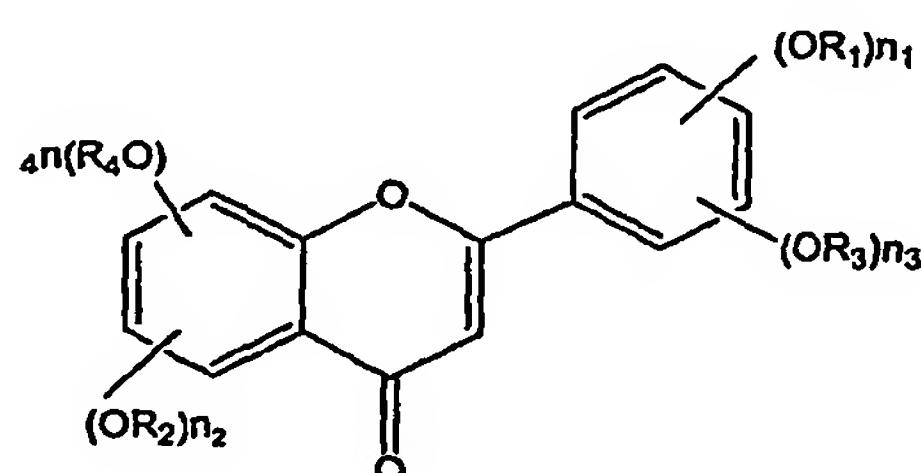
The ω -substituted C6 to C22 fatty acid is also represented by a saturated or unsaturated, linear or branched aliphatic chain (C6-C22) having two adjacent polar groups which are diol, dithiol, 1,2 and 1,3 dithiane, epoxide, such as thioctic acid.

20

Flavonoid esters of the invention

- 25 ➤ The esters of flavonoids with ω -substituted C6 to C22 fatty acids of the invention are characterized in that they correspond to formulas (I) to (X):

Flavone (I) :



(I)

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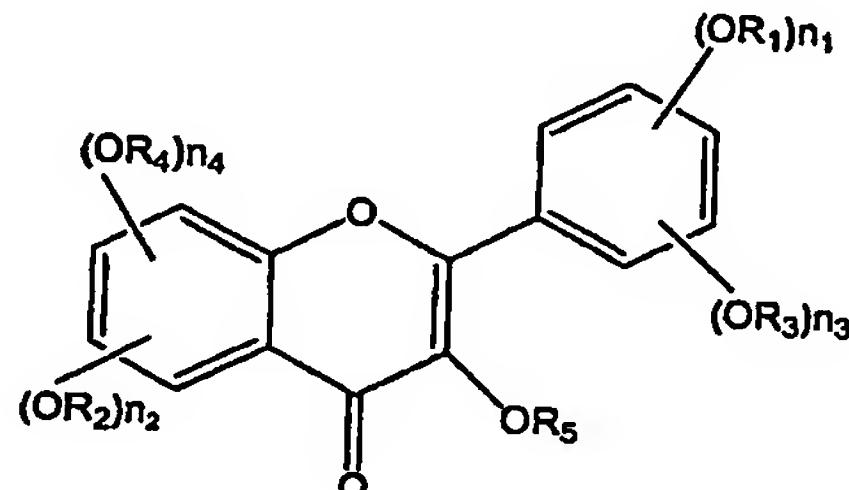
wherein :

- (g) the (OR_1) , (OR_2) , (OR_3) and (OR_4) groups are anywhere on the ring
 (h) R_1 and R_2 are identical to or different from each other and represent a hydrogen atom, a saturated or unsaturated, linear or branched alkyl radical ($C_1 - C_6$), a saturated or unsaturated, linear or branched acyl group with 1 to 6 carbon atoms, a monosaccharide or an oligosaccharide
 5 (i) R_3 and R_4 are identical to or different from each other and comprise a ω -substituted acyl group, or a monosaccharide or an oligosaccharide having at least one or more ω -substituted acyl groups, preferably from 1 to 6 acyl groups and more preferably from 1 to 3 acyl groups
 10 (j) n_1 and n_3 are identical to or different from each other, are numbers from 0 to 5, and the sum of $n_1 + n_2$ does not exceed 5
 (k) n_2 and n_4 are identical to or different from each other, are numbers from 0 to 4, and the sum of $n_3 + n_4$ does not exceed 4.

Examples of flavones are apigenin, luteolol as aglycon form and their glycosylated forms such as diosmin, orientin, saponarin and shaftoside.

The monosaccharide may preferably be substituted or unsubstituted glucose, rhamnose, galactose, arabinose or xylose. The oligosaccharide may preferably be the sugar moiety of the following flavonoids : tiliroside, orientin, shaftoside, saponarine, rutin, hesperidin, diosmin or a polymer of one or more monosaccharides previously described.

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Flavonol (II) :

(II)

wherein :

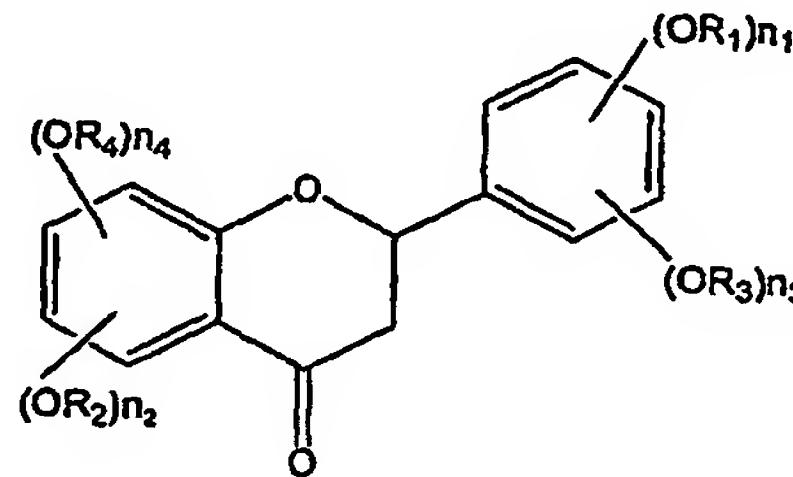
- 25 (l) the (OR_1) , (OR_2) , (OR_3) and (OR_4) groups are anywhere on the ring
 (m) R_1 and R_2 are identical to or different from each other and represent a hydrogen atom, a saturated or unsaturated, linear or branched alkyl radical ($C_1 - C_6$), a saturated or unsaturated, linear or branched acyl group with 1 to 6 carbon atoms, a monosaccharide or an oligosaccharide
 30 (n) R_3 , R_4 and R_5 are identical to or different from each other and comprise a ω -substituted acyl group, or a monosaccharide or an oligosaccharide having at least one

or more ω -substituted acyl groups, preferably from 1 to 6 acyl groups and more preferably from 1 to 3 acyl groups

- (o) n_1 and n_3 are identical to or different from each other, are numbers from 0 to 5, and the sum of $n_1 + n_3$ does not exceed 5
- 5 (p) n_2 and n_4 are identical to or different from each other, are numbers from 0 to 4, and the sum of $n_2 + n_4$ does not exceed 4.

Examples of flavonol are kaempferol, quercetin, rhamnetin as aglycon form and their glycosylated form as rutin, quercitrin, hyperoside and isoquercitrin.

Preferably the monosaccharide may be substituted or unsubstituted glucose, rhamnose, galactose, arabinose or xylose. Preferably the oligosaccharide may be the sugar moiety of the following flavonoids : tiliroside, orientin, schaftoside, saponarine, rutin, hesperidin, diosmin or a polymer of one or more monosaccharides previously described.



15 Flavanone (III) :

(III)

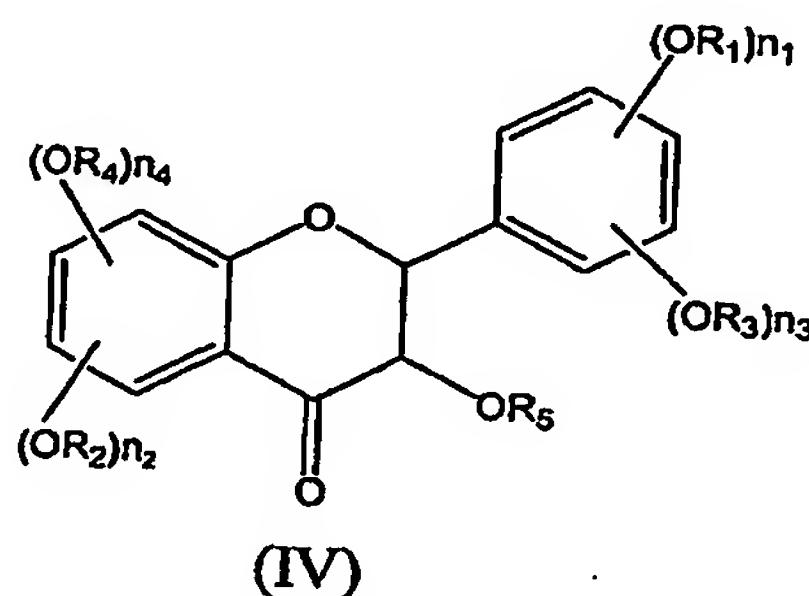
wherein :

- (q) the (OR_1) , (OR_2) , (OR_3) and (OR_4) groups are anywhere on the ring
- (r) R_1 and R_2 are identical to or different from each other and represent a hydrogen atom, a saturated or unsaturated, linear or branched alkyl radical ($C_1 - C_6$), a saturated or unsaturated, linear or branched acyl group with 1 to 6 carbon atoms, a monosaccharide or an oligosaccharide
- 20 (s) R_3 , R_4 and R_5 are identical to or different from each other and comprise a ω -substituted acyl group, or a monosaccharide or an oligosaccharide having at least one or more ω -substituted acyl groups, preferably from 1 to 6 acyl groups and more preferably from 1 to 3 acyl groups
- (t) n_1 and n_3 are identical to or different from each other, are numbers from 0 to 5, and the sum of $n_1 + n_3$ does not exceed 5
- 25 (u) n_2 and n_4 are identical to or different from each other, are numbers from 0 to 4, and the sum of $n_2 + n_4$ does not exceed 4.

Examples of flavanon are naringenin, eriodictyol, hesperetin, eucalyptin, cirsimarinin, cajaflavanon, hinokiklavon, amentaflavon, bilobetol as aglycon form and their glycosylated form such as hesperidin, neohesperidin, pruning or naringin.

- 5 Preferably the monosaccharide may be substituted or unsubstituted glucose, rhamnose, galactose, arabinose, xylose. Preferably the oligosaccharide may be the sugar moiety of the following flavonoids : tiliroside, orientin, schaftoside, saponarine, rutin, hesperidin, diosmin or a polymer of one or more monosaccharides previously described.

10 Flavonolol (IV) :



wherein :

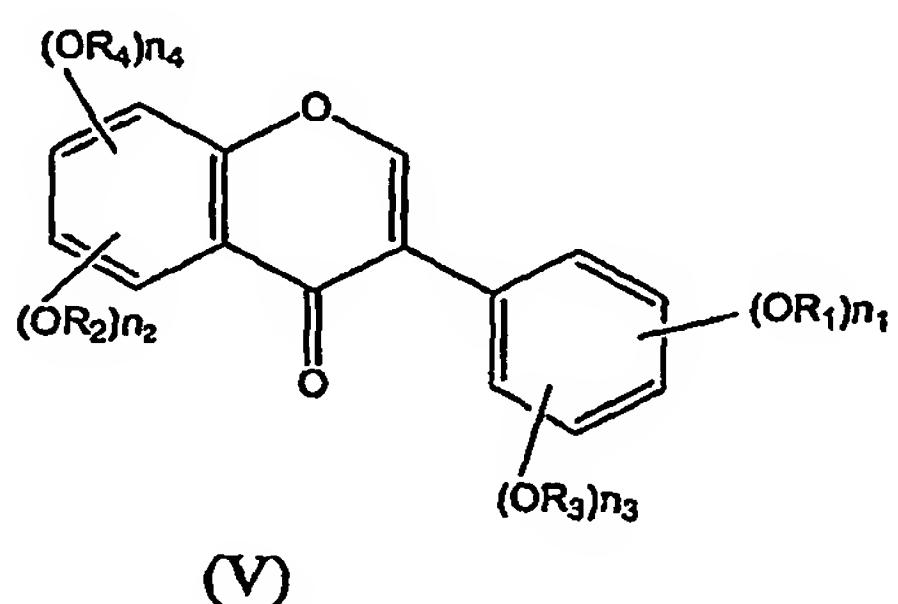
- (v) the (OR₁), (OR₂), (OR₃) and (OR₄) groups are anywhere on the ring
- (w) R₁ and R₂ are identical to or different from each other and represent a hydrogen atom, a saturated or unsaturated, linear or branched alkyl radical (C₁ – C₆), a saturated or unsaturated, linear or branched acyl group with 1 to 6 carbon atoms, a monosaccharide or an oligosaccharide
- (x) R₃, R₄ and R₅ are identical to or different from each other and comprise a ω -substituted acyl group, or a monosaccharide or an oligosaccharide having at least one or more ω -substituted acyl groups, preferably from 1 to 6 acyl groups and more preferably from 1 to 3 acyl groups
- (y) n₁ and n₃ are identical to or different from each other, are numbers from 0 to 5, and the sum of n₁ + n₃ does not exceed 5
- (z) n₂ and n₄ are identical to or different from each other, are numbers from 0 to 4, and the sum of n₂ + n₄ does not exceed 4.

Examples of flavonolol (also named dihydroflavonol) are fustin, garbanzol, taxifolin, 6-methoxytaxifolin, dihydrokaempferol and dihydrorobinetin as aglycon form and their glycosylated form.

Preferably the monosaccharide may be substituted or unsubstituted glucose, rhamnose, galactose, arabinose or xylose. Preferably the oligosaccharide may be a sugar moiety of the following flavonoids : tiliroside, orientin, schaftoside, saponarine, rutin, hesperidin, diosmin or a polymer of one or more monosaccharides previously described.

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Isoflavone (V) :

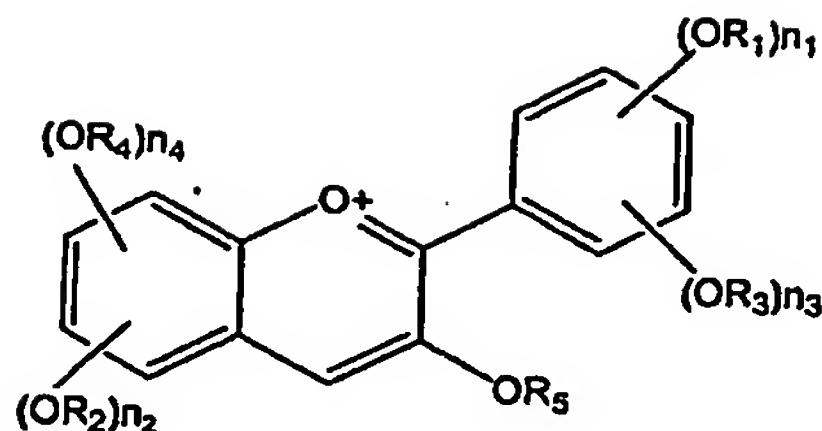


10 wherein :

- (aa) the (OR₁), (OR₂), (OR₃) and (OR₄) groups are anywhere on the ring
 - (bb) R₁ and R₂ are identical to or different from each other and represent a hydrogen atom, a saturated or unsaturated, linear or branched alkyl radical (C₁ – C₆), a saturated or unsaturated, linear or branched acyl group with 1 to 6 carbon atoms, a monosaccharide or an oligosaccharide
 - (cc) R₃ and R₄ are identical to or different from each other and comprise a ω -substituted acyl group, or a monosaccharide or an oligosaccharide having at least one or more ω -substituted acyl groups, preferably from 1 to 6 acyl groups and more preferably from 1 to 3 acyl groups
 - (dd) n₁ and n₃ are identical to or different from each other, are numbers from 0 to 5, and the sum of n₁ + n₃ does not exceed 5
 - (ee) n₂ and n₄ are identical to or different from each other, are numbers from 0 to 4, and the sum of n₂ + n₄ does not exceed 4.

25 Examples of isoflavonoids are daidzein, genistein, biochanin A, formonetin, cajanin, prunetin, irigenin, luteone as aglycon form and their glycosylated form as daidzin, genistin, iridin and puerarin.

30 Preferably the monosaccharide may be substituted or unsubstituted glucose, rhamnose, galactose, arabinose or xylose. Preferably the oligosaccharide may be the sugar moiety of the following flavonoids : tiliroside, orientin, schaftoside, saponarine, rutin, hesperidin, diosmin or a polymer of one or more monosaccharides previously described.



Anthocyanin (VI) :

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(VI)

wherein :

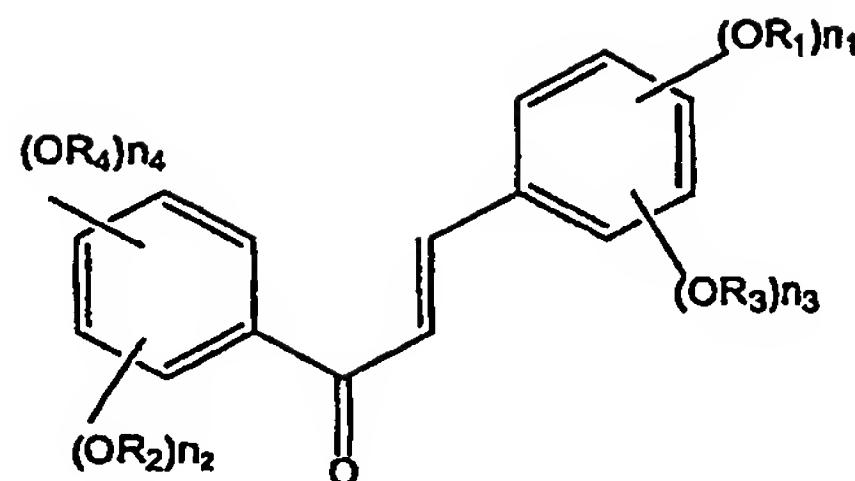
- (ff) the (OR₁), (OR₂), (OR₃) and (OR₄) groups are anywhere on the ring
- (gg) R₁ and R₂ are identical to or different from each other and represent a hydrogen atom, a saturated or unsaturated, linear or branched alkyl radical (C₁ – C₆), a saturated or unsaturated, linear or branched acyl group with 1 to 6 carbon atoms, a monosaccharide or an oligosaccharide
- (hh) R₃, R₄ and R₅ are identical to or different from each other and comprise a ω -substituted acyl group, or a monosaccharide or an oligosaccharide having at least one or more ω -substituted acyl groups, preferably from 1 to 6 acyl groups and more preferably from 1 to 3 acyl groups
- (ii) n₁ and n₃ are identical to or different from each other, are numbers from 0 to 5, and the sum of n₁ + n₃ does not exceed 5
- (jj) n₂ and n₄ are identical to or different from each other, are numbers from 0 to 4, and the sum of n₂ + n₄ does not exceed 4.

Examples of anthocyanins are cyanidin, 6-hydroxycyanidin, pelargonidin, okanin, malvidin as aglycon form and their glycosylated form as cyanidin-3-O-galactoside, cyanidin-3-O-rutinoside, pelargonidin or malvin.

25

Preferably the monosaccharide may be substituted or unsubstituted glucose, rhamnose, galactose, arabinose, xylose. Preferably the oligosaccharide may be the sugar moiety of the following flavonoids : tiliroside, orientin, schaftoside, saponarine, rutin, hesperidin, diosmin or a polymer of one or more monosaccharides previously described.

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Chalcone (VII) :

wherein :

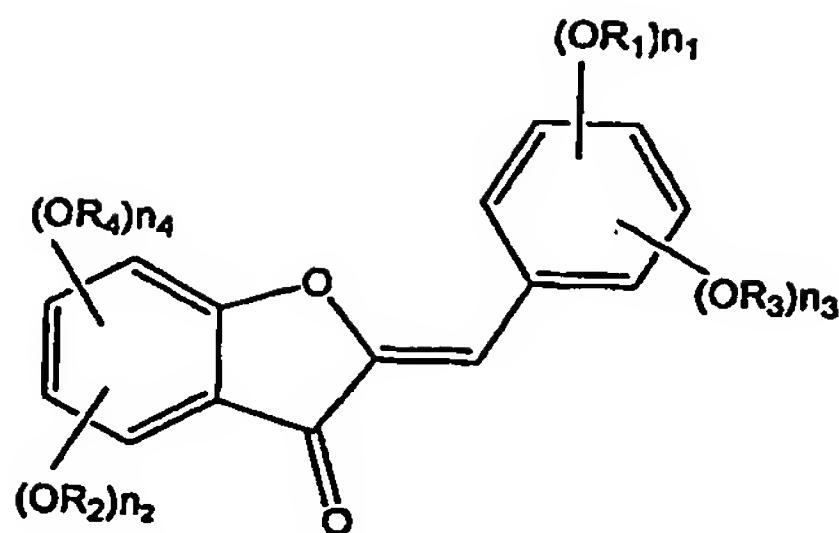
- (kk) the (OR₁), (OR₂), (OR₃) and (OR₄) groups are anywhere on the ring
- 5 (ll) R₁ and R₂ are identical to or different from each other and represent a hydrogen atom, a saturated or unsaturated, linear or branched alkyl radical (C₁ – C₆), a saturated or unsaturated, linear or branched acyl group with 1 to 6 carbon atom, a monosaccharide or an oligosaccharide
- 10 (mm) R₃ and R₄ are identical to or different from each other and comprise a ω -substituted acyl group, or a monosaccharide or an oligosaccharide having at least one or more ω -substituted acyl groups, preferably from 1 to 6 acyl groups and more preferably from 1 to 3 acyl groups
- (nn) n₁ and n₃ are identical to or different from each other, are numbers from 0 to 5, and the sum of n₁ + n₃ does not exceed 5
- 15 (oo) n₂ and n₄ are identical to or different from each other, are numbers from 0 to 5, and the sum of n₂ + n₄ does not exceed 5.

Examples of chalcones are davidigenin, phloretin, isoliquiritigenin as aglycon form and their glycosylated form as phloridzin and glycyphyllin.

20

Preferably the monosaccharide may be substituted or unsubstituted glucose, rhamnose, galactose, arabinose or xylose. Preferably the oligosaccharide may be the sugar moiety of the following flavonoids : tiliroside, orientin, schaftoside, saponarine, rutin, hesperidin, diosmin or a polymer of one or more monosaccharides previously described.

25



Aurone (VIII) :

(VIII)

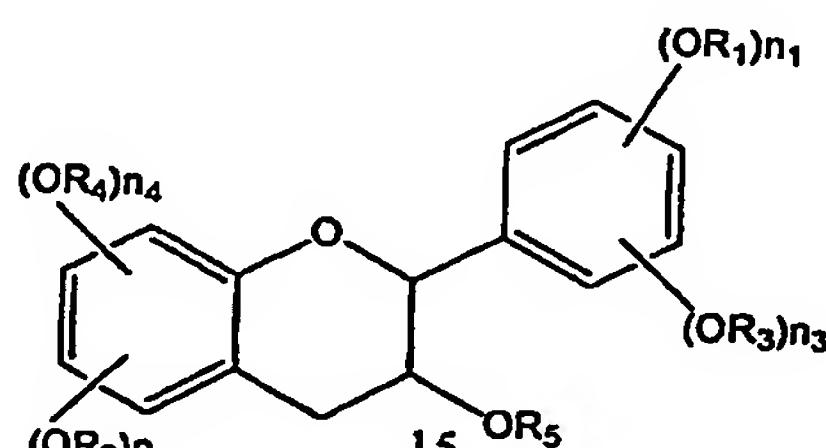
wherein :

- 5 (pp) the (OR₁), (OR₂), (OR₃) and (OR₄) groups are anywhere on the ring
- (qq) R₁ and R₂ are identical to or different from each other and represent a hydrogen atom, a saturated or unsaturated, linear or branched alkyl radical (C₁ – C₆), a saturated or unsaturated, linear or branched acyl group with 1 to 6 carbon atom, a monosaccharide or an oligosaccharide
- 10 (rr) R₃ and R₄ are identical to or different from each other and comprise a ω -substituted acyl group, or a monosaccharide or an oligosaccharide having at least one or more ω -substituted acyl groups, preferably from 1 to 6 acyl groups and more preferably from 1 to 3 acyl groups
- 15 (ss)n₁ and n₃ are identical to or different from each other, are numbers from 0 to 5, and the sum of n₁ + n₃ does not exceed 5
- (tt) n₂ and n₄ are identical to or different from each other, are numbers from 0 to 4, and the sum of n₂ + n₄ does not exceed 4.

20 Examples of aurones are aureusidin, sulphuretin, hispidol as aglycon form and their glycosylated form as 6-glucoside-hispidol.

25 Preferably the monosaccharide may be substituted or unsubstituted glucose, rhamnose, galactose, arabinose or xylose. Preferably the oligosaccharide may be the sugar moiety of the following flavonoids: tiliroside, orientin, schaftoside, saponarine, rutin, hesperidin, diosmin or a polymer of one or more monosaccharides previously described.

Flavanol (IX) :



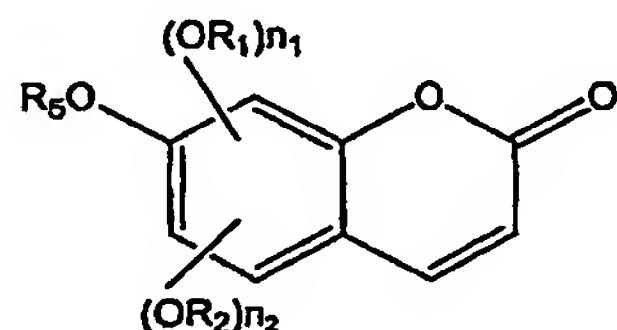
(IX)

wherein :

- 5 (uu) the (OR₁), (OR₂), (OR₃) and (OR₄) groups are anywhere on the ring
- (vv) R₁ and R₂ are identical to or different from each other and represent a hydrogen atom, a saturated or unsaturated, linear or branched alkyl radical (C₁ – C₆), a saturated or unsaturated, linear or branched acyl group with 1 to 6 carbon atoms, a monosaccharide or an oligosaccharide
- 10 (ww) R₃, R₄ and R₅ are identical to or different from each other and comprise a ω -substituted acyl group, or a monosaccharide or an oligosaccharide having at least one or more ω -substituted acyl groups, preferably from 1 to 6 acyl groups and more preferably from 1 to 3 acyl groups
- (xx) n₁ and n₃ are identical to or different from each other, are numbers from 0 to 5, and the sum of n₁ + n₃ does not exceed 5
- 15 (yy) n₂ and n₄ are identical to or different from each other, are numbers from 0 to 4, and the sum of n₂ + n₄ does not exceed 4.

Examples of flavanol (flavan-3-ols) are catechin, epicatechin, fisetinidol as aglycon form and their glycosylated form as catechin-7-O-xyloside, cyanidin-3-O-rutinoside, pelargonidin or malvin.

Preferably the monosaccharide may be substituted or unsubstituted glucose, rhamnose, galactose, arabinose or xylose. Preferably the oligosaccharide may be the sugar moiety of the following flavonoids : tiliroside, orientin, schaftoside, saponarine, rutin, hesperidin, diosmin or a polymer of one or more monosaccharides previously described.



Hydroxycoumarin (X) :

30

(X)

wherein :

- (zz) the (OR₁) and (OR₂) groups are anywhere on the ring

- (aaa) R_1 represents a hydrogen atom, a saturated or unsaturated, linear or branched alkyl radical ($C_1 - C_6$), a saturated or unsaturated, linear or branched acyl group with 1 to 6 carbon atom, a monosaccharide or an oligosaccharide
- 5 (bbb) R_2 and R_5 are identical to or different from each other and comprise a ω -substituted acyl group, or a monosaccharide or an oligosaccharide having at least one or more ω -substituted acyl groups, preferably from 1 to 6 acyl groups and more preferably from 1 to 3 acyl groups
- (ccc) n_1 and n_2 are identical to or different from each other, are numbers from 0 to 3, and the sum of $n_1 + n_2$ does not exceed 3.

10

Examples of hydroxycoumarins are esculetin, umbelliferone, scopoletin, fraxetin as aglycon form and their glycosylated form as esculin, cichoriine or fraxin.

15 Preferably the monosaccharide may be substituted or unsubstituted glucose, rhamnose, galactose, arabinose, xylose. Preferably the oligosaccharide may be the sugar moiety of the following flavonoids : tiliroside, orientin, schaftoside, saponarine, rutin, hesperidin, diosmin or a polymer of one or more monosaccharides previously described.

20 **Preparation of the flavonoid esters**

25 ➤ The flavonoid esters according to the invention may be synthesized using known acylation processes from the state of the art. The acylation can be performed using an enzymatic process as described in the recently filed patent application no. EP 02292960.9 (Cognis France). The esters can also been obtained by chemical acylation methods. Chemical acylation agent may be chosen among acids of formula $RCOOH$, the halogen derivatives of these acids $RCOHal$, anhydrides of formula $RCOOCR$ or esters of formula $RCOOR'$ wherein R' is a C_1-C_6 alkyl group, in an anhydric appropriate solvent under inert atmosphere. Appropriate solvents may be chosen from the group consisting of toluene, pyridine, chloroform, tetrahydrofuran and acetone.

Examples

Example 1: Synthesis of ester of rutin with octadecanoic acid

5

This reaction was carried out in a 250 ml batch reactor. Rutin (0.85 g, 1.4 mmol) and octadecanoic acid (0.97 g, 3.1 mmol) were dissolved in 250 ml *tert*-amyl alcohol. The medium was heated at 60°C under vacuum (170 mbar). The resulting vapor was condensed and recycled to the reactor through a column filled with molecular sieves (50 g). This procedure allowed a low water level (< 100 mM) in the reactor after 21 h. 2.5 g of the lipase of *Candida antarctica* (Novozym 435) was then added which is a lipase immobilized on a macroporous acrylic resin with an activity of 7000 PLUG-1 (Propyl Laurate Synthesis).

10

After 70 h the enzyme was recovered by filtration. The medium was then concentrated by evaporation of solvent. Two systems of extraction were used to eliminate the residual substrates. A mixture of acetonitrile / heptane (3/5 v/v) is used to remove the palmitic acid, while the separation of rutin was carried out by an extraction with water / heptane (2/3 v/v).

The ^1H NMR of the ester obtained was :

^1H NMR : (400 MHz, DMSO d_6) : 0.76 (d, 3H), 1.2 (m, 24H), 1.44 (m, 4H), 2.17 (m, 4H), 3.1-3.5 (broad, 8H), 3.7 (d, 1H), 4.45 (s, 1H), 4.65 (t, 1H), 5.44 (d, 1H), 6.19 (d, 1H), 6.36 (d, 1H), 6.83 (d, 1H), 7.5 (m, 2H) ppm.

Example 2: Synthesis of ester of rutin with hexadecanoic acid

25

The acylation of rutin (0.8 g, 1.3 mmol) with hexadecanoic acid (0.98 g, 3.4 mmol) was carried out as described in example 1.

After 63 hours of reaction time the same procedure of purification by liquid-liquid extraction as described in example 1 allowed the recovery of rutin hexadecanoate.

30

The ^1H NMR of the ester obtained was :

^1H NMR : (400 MHz, DMSO d_6) : δ 0.76 (d, 3H), 1.2 (m, 60H), 1.5 (m, 12H), 2.2 (m, 12H), 3.1-3.6 (broad, 8H), 3.7 (d, 1H), 4.45 (s, 1H), 4.65 (t, 1H), 5.43 (d, 1H), 6.18 (d, 1H), 6.36 (d, 1H), 6.84 (d, 1H), 7.50 (m, 2H) ppm.

35

Example 3: Synthesis of ester of rutin with azelaic acid

The acylation of rutin (0.8 g, 1.3 mmol) with azelaic acid (0.58 g, 3.1 mmol) was carried out as described in example 1.

- 5 After 55 hours of reaction time the enzyme was filtered. The medium was then concentrated by evaporation of solvent. The ester was recovered by two systems of extraction. A mixture of water/heptane (2/3 v/v) was used to remove azelaic acid. The recovery of the ester was carried out by extraction with ethyl acetate.
- 10 The ^1H NMR of the ester obtained was :
 ^1H NMR : (400 MHz, DMSO d_6) : δ 0.75 (d, 3H), 1.24 (m, 12H), 1.48 (m, 8H), 2.20 (m, 8H), 3.15-3.50 (broad, 8H), 3.68 (d, 1H), 4.46 (s, 1H), 4.65 (t, 1H), 5.43 (d, 1H), 6.19 (d, 1H), 6.37 (d, 1H), 6.84 (d, 1H), 7.50 (m, 2H), 12.6 (s, 1H, C₅-OH) ppm

15

Example 4: Synthesis of ester of rutin with 11-mercaptoundecanoic acid

The acylation of rutin (0.7 g, 1.2 mmol) with 11-mercaptoundecanoic acid (0.7 g, 3.1 mmol) was carried out as described in example 1.

- 20 After 64 hours of reaction time the enzyme was filtered. The solvent was then evaporated and the product was dissolved in methanol. The ester is recovered by two systems of extraction. A mixture of water/heptane (2/3 v/v) is used to remove the acid and the recovery of the ester was carried out by extraction with dichloromethane.
- 25 The ^1H NMR of the ester obtained was :
 ^1H NMR : (400MHz, DMSO d_6) : δ 0.76 (d, 3H), 1.04 (d, 1H), 1.2 (m, 24H), 1.5 (m, 4H), 1.6 (m, 2H), 2.15 (m, 2H), 2.28 (m, 1H), 2.50 (m, 1H), 2.68 (m, 2H), 3.1-3.9 (broad), 4.45 (s, 1H), 4.55 (m, 1H), 4.65 (t, 1H), 5.07 (d, 1H), 5.12 (d, 1H), 5.28 (d, 1H), 5.44 (d, 1H), 6.2 (s, 1H), 6.37 (s, 1H), 6.84 (d, 1H), 7.46 (m, 2H)

30

Example 5: Acylation of naringin with octadecanoic acid

The acylation of naringin (0.59 g, 1 mmol) with octadecanoic acid (0.98 g, 3.1 mmol) was carried out as described in example 1.

- 35 After 50h of reaction time the same procedure of purification by extraction as described in example 1 allowed the recovery of the ester.

Example 6: Synthesis of ester of esculin with octadecanoic acid

The acylation of esculin (0.42 g, 1.2 mmol) with octadecanoic acid (0.97 g, 3.1 mmol) was carried out as described in example 1.

- 5 After 50 h of reaction time the same procedure of purification by extraction as described in example 1 allowed the recovery of ester.

The structure was confirmed by ^1H NMR:

10 ^1H NMR : (400 MHz, DMSO d_6) : 1.2 (m, 24H), 1.5 (m, 4H), 2.2 (m, 4H) 3.15-3.55 (broad, 2H), 3.61 (t, 1H), 4.11 (dd, 1H), 4.34 (dd, 1H), 4.84 (d, 1H), 6.2 (d, 1H), 6.8 (s, 1H), 7.3 (s, 1H), 7.83 (d, 1H) ppm.

Example 7: Synthesis of ester of esculin with thioctic acid

15

The acylation of esculin (0.87 g, 2.5 mmol) with thioctic acid (1.23 g, 6 mmol) was carried out as described in example 1.

- 20 After 70 hours of reaction time the enzyme was filtered. The medium was then concentrated by evaporation of solvent. The ester was recovered by two systems of extraction. A mixture of water/heptane/acetonitrile (2/3/0.4 v/v/v) was used to remove thioctic acid and the recovery of ester was carried out by extraction with dichloromethane.

The structure was confirmed by ^1H NMR.

25 ^1H NMR : (400 MHz, DMSO d_6): 1.2-1.9 (broad, 8H), 2.1-2.4(broad, 4H), 3.2 (m, 2H), 3.5 (m, 1H), 3.7 (m, 1H), 4.12 (dd, 1H), 4.35 (d, 1H), 4.85 (d, 1H), 5.23 (d, 1H), 5.33 (d, 1H), 6.26(d, 1H), 6.84 (s, 1H), 7.33 (s, 1H), 7.86 (d, 1H) ppm.

Example 8 - UVA cytoprotection, anti-oxidative effect

30

- The cytoprotection against UVA irradiation has been evaluated by a test on human fibroblasts because UVA radiation penetrates the epidermis until the dermis where it induces oxidative stress, mainly by activation of photosensitising biological components, which catalyse the formation of ROS like anion superoxide, hydrogen peroxide and singlet oxygen, and lipoperoxidation of the cell membrane. These oxidative stress effects are evaluated in vitro due to measuring of the level of released MDA (malondialdehyde) and of intracellular GSH (reduced glutathione) (Morlière P., Moisan A., Santus R., Huppe G., Mazière J.C., Dubertret L.: UV-A

induced lipid peroxydation in cultured human fibroblasts. *Biochim. Biophys. Acta* (1991) 1084, 3:261-269).

The lipoperoxides formed after UVA irradiation undergo a decay into malondialdehyde which can form cross-links between many biological molecules like proteins with inhibition of enzymes and nucleic bases with risk of mutagenesis. The Glutathione (GSH) is a peptide produced by the cells to protect them from oxidative stress or certain pollutants like mercury or lead. An increase in the GSH level enhances the activity of glutathion-S-transferase, a detoxification enzyme. GSH is evaluated according to the method of Hissin (Hissin P.J., Hilf R. A fluorometric method for determination of oxydised and reduced Glutathione in tissus. *Analytical Biochemistry* (1977) vol 74, pp 214-226).

Human fibroblasts were inoculated with growth medium (DMEM+FCS) and incubated 3 days at 37°C, with 5% CO₂. The growth medium was then exchanged with a medium containing an ingredient to be tested and incubated 2 days at 37°C with CO₂=5%. After the exchange of medium with balanced salt solution, the cell culture was irradiated by UVA 20J/cm². Cell proteins and GSH were measured, and MDA released in the supernatant was determined spectrophotometrically.

Table 1

Results in % against control (mean on 2-3 assays in triplica):

Product	Dose % w/v	MDA re- leased	Cell pro- teins	Cell GSH/protein ratio
Control (not irradiated)	-	0	100	100
Control / UVA (20 J/cm ²)	-	100	107	78
Rutin	0.003	79	126	72
	0.01	72	128	71
Rutin octadecandoate according to example 1	0.001	46	139	73
	0.003	15	133	122
Rutin hexadecandoate according to example 2	0.003	46	129	101
	0.01	21	178	75
Rutin azelaiate according to example 3	0.001	78	144	67
	0.003	64	165	64
Rutin 11-mercaptoundecanoate according to example 4	0.001	34	94	131
	0.003	0	89	283

rutin was purchased from Sigma.

The UVA irradiation has induced a release of MDA and a decrease of cell GSH. After incubation of the fibroblast with esters of rutin, a strong protection of cells against UVA-induced MDA released and GSH decrease was obtained, whereas rutin had protected the fibroblasts
5 very poorly.

Example 9. UVB- cytoprotection and anti-inflammatory effect

- 10 The arachidonic cascade is an important mechanism of cutaneous inflammation. This cascade may be induced by several factors, particularly by UVB irradiation. UVB induces the inflammatory response by activation of phospholipase A2 (PLA2), which results in a release of arachidonic acid from cell membranes. Then other specific enzymes (so called cyclo-oxygenases) transform arachidonic acid in active components called prostaglandin (PG) which are secreted
15 from the cells. The fixation of certain prostaglandins (PGE2) on specific skin receptors is followed by redness and the swelling of human skin. On cultured human cells , these UVB effects on cell's membrane are associated with a release of a cytoplasmic enzyme into the supernatant medium: Lactate Dehydrogenase or LDH.
- 20 Human keratinocytes were inoculated with a growth medium (DMEM+FCS) and incubated for 3 days at 37°C and 5% CO₂. The growth medium was then exchanged with balanced salt solution containing the ingredient to be tested, the cell culture was irradiated by UVB 50 mJ/cm² (DUKE GL40E lamp). After 1 day of incubation at 37°C with 5% CO₂, LDH and PGE2 released in the medium were determined, and cellular DNA was measured using a fluorescent probe to determine the cell viability.
25

Table 2

Results in % against control (mean on 2-3 assays in triplicata):

<u>Product</u>	<u>Dose</u> % w/v	Keratinocytes DNA	LDH released	PGE2 released
Control (not irradiated)	-	100	0	0
Control / UVB (50mJ/cm ²)	-	23	100	100
Rutin	0.03	69	17	0
	0.1	73	18	10
	0.001	23	73	28
Rutin octadecadioate according to example 1	0.003	49	31	3
	0.003	24	53	2
	0.01	39	19	0
Rutin hexadecadioate according to example 2	0.003	51	45	28
	0.01	53	27	19
	0.0001	44	75	26
Rutin 11-mercaptoundecanoate according to example 4	0.0003	41	92	12

5 Rutin was purchased from Sigma.

10 The UVB irradiation has induced an inflammation with a release of PGE2 and with cell membrane injury as demonstrated by the release of LDH activity in the medium, and a decrease of the keratinocytes cell number (decrease of around 77% of cell DNA). After incubation of the keratinocytes with rutin or the esters of rutin with ω -substituted fatty acid, and UVB irradiation, an increase of viable cells and a decrease of released LDH and PGE2 was obtained. But the esters of rutin are effective at doses 3-100 times lower than the active doses of rutin. These results demonstrate the anti-inflammatory efficiency of the tested products and their ability to protect cells from the damages induced by UVB irradiation.

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Claims

1. Flavonoid esters with ω -substituted C6 to C22 fatty acids.
- 5 2. Flavonoid esters according to claim 1, characterised in that the flavonoid is an aglycone or the glycosylated form of polyphenols chosen from the group consisting of flavones, flavonols, flavanones, flavanols, flavanolols, isoflavones, anthocyanins, proanthocyanidins, chalcones, aurones and hydroxycoumarines.
- 10 3. Flavonoid esters according to claim 1 or 2, characterised in that the ω -substituted C6 to C22 fatty acid is a saturated or unsaturated, linear or branched aliphatic C6 to C22 - carboxylic acid having one or more polar groups.
4. Flavonoid esters according to claim 3, characterised in that the polar group is on the terminal carbon atom of the C6 to C22 – carboxylic acid.
- 15 5. Flavonoid esters according to claims 1 to 4, characterised in that the polar group of the ω -substituted C6 to C22 fatty acid is a derivative of carboxylic acid chosen from the group consisting of a carboxylic acid COOH; an amide CONR₂' or CONR₃'S⁻ wherein R' is a hydrogen atom, a saturated or unsaturated, linear or branched alkyl C1-C6 radical, or an aryl, aralkyl or aralkylene radical and S⁻ a counter ion; a COHal where Hal is a halogen atom and a COSH.
- 20 6. Flavonoid esters according to claim 5, characterised in that the ω -substituted C6 to C22 fatty acid is a dicarboxylic acid.
7. Flavonoid esters according to claim 6, characterised in that the ω -substituted C6 to C22 fatty acid is chosen from the group consisting of octanedioic acid, azelaic acid, decandioic acid, dodecandioic acid, hexadecandioic acid and octadecandioic acid.
- 25 8. Flavonoid esters according to claims 1 to 4, characterised in that the ω -substituted C6 to C22 fatty acid is a dicarboxylic acid linked to a flavonoid by an ester bond on one of its carboxylic group HOOC-X-C(=O)-O-Flavonoid, wherein X is a saturated or unsaturated, linear or branched alkyl radical (C₄ – C₂₀).
9. Flavonoid esters according to claims 1 to 4, characterised in that the polar group of the ω -substituted C6 to C22 fatty acid is a thiol or an alkylthioalkyl group.
- 30 10. Flavonoid esters according to claim 9, characterised in that the ω -substituted C6 to C22 fatty acid is 11-mercaptoundecanoic acid.
11. Flavonoid esters according to claims 1 to 4, characterised in that the ω -substituted C6 to C22 fatty acid is having two adjacent polar groups which are diol, dithiol, 1,2 and 1,3 dithiane or epoxide.
- 35 12. Flavonoid esters according to claim 11, characterised in that the ω -substituted C6 to C22 fatty acid is thioctic acid.

13. A nutritional or cosmetic or pharmaceutical composition containing flavonoid esters according to claims 1 to 12.
14. A nutritional or cosmetic or pharmaceutical composition comprising liposomes or microcapsules containing flavonoid esters according to claims 1 to 12.
- 5 15. A nutritional or cosmetic or pharmaceutical composition according to claims 13 or 14, characterised in that it contains 0.0001 to 10 wt % of the flavonoid esters based on the final composition.
16. The use of flavonoid esters according to claims 1 to 12 as cosmetic agents to protect skin and scalp against damages caused by UV and IR radiation.
- 10 17. The use of flavonoid esters according to claims 1 to 12 as cosmetic agents to protect skin and scalp against mitochondrial or nuclear DNA damages caused by UV radiation.
18. The use of flavonoid esters according to claims 1 to 12 as anti-inflammatory and/or soothing and relieving agents.
- 15 19. The use of flavonoid esters according to claims 1 to 12 as cosmetic agents against the ageing of skin and scalp.
20. The use of flavonoid esters according to claims 1 to 12 as cosmetic agents to improve sensitive skin and to reduce scalp itching.
21. The use of flavonoid esters according to claims 1 to 12 as cosmetic agents to modify the melanin synthesis in human skin.
- 20 22. The use of flavonoid esters according to claims 1 to 12 for the production of a preparation for stimulating the metabolism and the immune defense of the human skin, more particularly for defense against oxidative stress.
23. The use of flavonoid esters according to claims 1 to 12 for the production of a preparation against environmental stress or pollutants.
- 25 24. The use of flavonoid esters according to claims 1 to 12 for the production of an dermatological anti-inflammatory care preparation.
24. The use of flavonoid esters according to claims 1 to 12 in sun protection compositions.
25. The use according to claims 16 to 24, characterised in that the flavonoid esters are used in quantities of 0,0001 to 10 wt % based on the final composition.
- 30 26. The use according to claims 16 to 25, characterised in that the flavonoid esters are incorporated in microcapsules or liposomes.

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Summary

- 5 The invention refers to esters of flavonoids such as flavones, flavonols, flavanones, flavanols, flavanolols, isoflavones, anthocyanins, proanthocyanidins, chalcones, aurones and hydroxycoumarins conjugated by an ester bond to an ω -substituted C6-C22 fatty acid. These flavonoid derivatives exhibit excellent skin protecting properties, particularly against damages due to UV-radiation. They show a very good chemical stability and are easily incorporated into cosmetic and pharmaceutical formulations.
- 10